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Original article

Heavy/light chain specific immunoglobulin ratios provides no additional information than serum proteins electrophoresis and immunofixation for the diagnosis and the follow-up of intact immunoglobulin multiple myeloma patients

Intérêt du dosage de l'immunoglobuline monoclonale complète lors du diagnostic ou du suivi des patients présentant un myélome à immunoglobuline complète : l'électrophorèse des protéines sériques et l'immonofixation ne seraient-elles pas suffisantes ?

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ABSTRACT

Background. – Serum protein electrophoresis (SPE) and immunofixation electrophoresis (IFE) are used for diagnosis and follow-up of patients with intact immunoglobulin multiple myeloma. However, the numerous limitations of these methods led to the development of a nephelometric immunoassay (Hevylite™) for the specific measurement of serum IgGκ, IgGλ, IgAκ and IgAλ concentrations.
Methods. – In this study, we evaluated the correlation between this assay and SPE and IFE in 114 sera of 15 patients (12 IgG and 3 IgA patients) and its impact on the clinical care of patients, especially for diagnosis, for the evaluation of residual disease and for early detection of relapse.
Results. – At inclusion and during follow-up, we found a good correlation between monoclonal immunoglobulin concentrations and SPE (R^2 = 0.902 for IgA and R^2 = 0.915 for IgG) and nephelometric quantification (R^2 = 0.948 for IgA and R^2 = 0.920 for IgG) for the evaluation of monoclonal and polyclonal immunoglobulins. Our results illustrate that the Hevylite™ test is less sensitive than the IFE for detection of residual disease: 5 patients who obtained very good partial response or complete response had normalization of the Hevylite™ ratio while IFE was still positive. A relapse had been detectable with the Hevylite™ ratio 1 to 2 months earlier than with SPE and IFE in 3 patients out of 15, but no recommendations for treating patients with only slight biological relapse are available.
Conclusion. – Our results demonstrate that heavy/light chain specific immunoglobulin ratios provides no additional information than serum proteins electrophoresis and immunofixation for the diagnosis and the follow-up of intact immunoglobulin multiple myeloma patients. We also studied the correlation between the concentration of total immunoglobulin measured by Hevylite™ (sum of Ig'κ + Ig'λ) and nephelometric measurement of total IgG or IgA. For this correlation analysis, all 114 sera were analyzed. The correlation coefficient was R^2 = 0.948 for IgA and R^2 = 0.920 for IgG.

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RÉSUMÉ

L'électrophorèse (SPE) et l'immunofixation (IFE) des protéines sériques sont utilisées pour le diagnostic et le suivi des patients atteints de myélome multiple à immunoglobuline intacte. Ces techniques présentent certaines limites justifiant le développement d'une méthode de dosage néphélémétrique de l'immunoglobuline complète (Ig'κ, Ig'λ) (Hevylite™). Cette étude évalue la corrélation entre ce dosage et la SPE et l'IFE sur 114 sérums de 15 patients (12 IgG et 3 IgA) et son impact sur la prise en charge des patients, au diagnostic, à l'évaluation de la maladie résiduelle et pour la détection de la rechute précoce. Au diagnostic et au cours du suivi, il existe une bonne corrélation entre le dosage Hevylite™ et SPE (R^2 = 0,902 pour IgA et R^2 = 0,915 pour IgG) et entre le dosage Hevylite™ et la concentration totale en Ig G ou A (R^2 = 0,948 pour IgA et R^2 = 0,920 pour IgG). Le test Hevylite™ semble moins sensible que l'IFE pour la détection de la maladie résiduelle : 5 patients qui ont obtenu une très bonne réponse partielle ou une réponse complète par normalisation du rapport Hevylite™ tandis que l'IFE était encore positive. Une rechute était détectable avec le rapport Hevylite™ 1 à 2 mois plus tôt que via la SPE et l'IFE pour 3 patients sur 15. Ainsi, le dosage de l'immunoglobuline monoclonale complète ne fournit aucune information supplémentaire par rapport à la SPE et l'IFE pour le diagnostic et le suivi des patients atteints de myélome à immunoglobulines intactes. À ce jour, il n'existe aucune recommandation concernant le traitement des patients présentant une rechute biologique seule.

1. Introduction

The diagnosis of multiple myeloma (MM) requires the presence of monoclonal immunoglobulin in serum and/or urine, increased numbers of bone marrow plasma cells and related organ or tissue impairment (bone lesions, hypercalcemia, anemia, renal failure) [1]. Over the past 20 years, introduction of more effective treatments has achieved higher response rates of greater than 80% [2]. Several studies have shown that complete response defined by International Myeloma Working Group (IMWG) criteria is associated with improved survival [3,4].

In routine practice, serum protein electrophoresis (SPE), serum immunofixation electrophoresis (IFE) and/or measurement of polyclonal immunoglobulin (Ig) concentrations by immunochemical assays are used for diagnosis and follow-up of patients with intact immunoglobulin multiple myeloma. However, there are several limitations with these methods. Although SPE is a simple and inexpensive method, it is not very sensitive [5]. This is particularly true for low concentrations of monoclonal Ig that co-migrate with proteins located in the alpha- or beta-globulin regions, making their quantification impossible by SPE. Consequently, the quantification of low concentrations of monoclonal immunoglobulin (lower to 3.0 g/L) by SPE is not very accurate [6,7]. Improved sensitivity is achieved through IFE which allows determination of the isotype of the monoclonal component, but this technique is not quantitative. Immunochemical assays using specific antibodies are available for the quantification of polyclonal and monoclonal Ig. Even though measurement of Ig by nephelometry is reliable at physiological concentrations of polyclonal Ig, it may over-estimate the concentration of monoclonal immunoglobulin [8,9]. Nevertheless, determination of monoclonal immunoglobulin by quantification of protein bands on SPE is considered to be the best biomarker for monitoring and evaluation of response to treatment. It appears to be essential, therefore, to improve analytical methods in order to monitor response and to assess residual disease.

The introduction of antibodies which bind to conformational epitopes spanning the junctional regions between bound κ or λ light chains and their respective heavy chain partners has allowed the development of a nephelometric immunoassay (Hevylite™ – Binding Site Group Ltd) for specific measurement of serum IgGκ, IgGλ, IgAκ, IgAλ, IgMκ and IgMλ concentrations [10]. This assay enables calculation of IgGκ/IgGλ, IgAκ/IgAλ and IgMκ/IgMλ ratios (heavy/light chain [HLC] ratios) for individual patients. Quantification of the involved and uninvolved heavy/light chains in serum may provide an accurate and quantifiable measurement of the tumor burden. Three studies have demonstrated that HLC ratios at diagnosis correlate with progression free survival [11] and overall survival [12,13]. Nevertheless, a very limited number of studies have evaluated the potential value of these tests for assessment of response in multiple myeloma patients, suggesting that HLC ratios could be more relevant for evaluation of minimal residual disease [12,14]. The aim of our study was to evaluate in clinical practice whether the Hevylite™ test could provide additional information to SPE and IFE during the follow-up of patients with intact immunoglobulin multiple myeloma. To address this issue, we initially evaluated the correlation between the concentration of monoclonal Ig determined by the Hevylite™ test and by the monoclonal spike (M-spike) by SPE. We also assessed the additional value of the Hevylite™ test for evaluation of residual disease and early detection of relapse.

2. Patients and methods

2.1. Inclusion criteria and study design

Patients were prospectively included if they had intact immunoglobulin IgG or IgA multiple myeloma requiring treatment, irrespective of the number of lines of treatment. Patients were recruited from a single internal medical department at the Rennes University Hospital (France) and were followed for a period ranging from 5 to 12 months (132–363 days). Patients with intact IgM and IgD multiple myeloma, light chain or non-secretory multiple myeloma were excluded from the study.

Demographic data (age, sex), clinical (diagnostic or relapse, treatment) and laboratory parameters (hemoglobin, leucocytes, creatinine, calcemia, concentration of β2 microglobulin) were prospectively recorded.

Evaluation of treatment response was achieved from samples obtained on the first day of each chemotherapy cycle (day-1), by quantifying the monoclonal component using SPE if the peak was measurable [15]. HLC ratio results, M-spike, IgG or IgA concentrations were measured on day-1 of each chemotherapy cycle. IFE was carried out initially for all included patients to characterize and identify the isotype, and in order to allow subsequent evaluation of the response.

For each included patient, after routine follow-up biochemical analyses on serum samples, the surplus sera were stored in a sera bank so that no additional blood sampling was necessary. Informed consents of patients were obtained. The study was approved by the appropriate ethics committee: the sera bank has been declared to the Committee for the Protection of Persons (CPP) of Rennes, France and the National Commission on Informatics and Liberties (CNIL).

2.2. Laboratory methods

Serum protein electrophoresis was performed on Capillarys® (Sebia) according to manufacturer's recommendations. Monoclonal compound was evaluated by integrated the valley-valley area under the curve (AUC).